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Relation of Dimensionless Index to Long-Term Outcome in Aortic Stenosis With Preserved LVEF

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CME Objective for This Article: After reading this article the reader should be able to: 1) review the Doppler-echocardiography parameters routinely used for the evaluation of aortic valve stenosis; 2) understand the pitfalls in the echocardiographic quantification of stenosis severity in a difficult scenario of aortic valve stenosis; and 3) review the contribution of dimensionless index for the assessment of aortic stenosis severity and to understand its advantages and prognostic value.

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Relation of Dimensionless Index to Long-Term Outcome in Aortic Stenosis With Preserved LVEF

ABSTRACT

OBJECTIVES The aim of this study was to assess the role of the dimensionless index (DI) in a registry of patients with aortic stenosis (AS) to objectively establish prognostic DI thresholds for various degrees of AS severity.

BACKGROUND DI is a classic marker of severity in AS that does not rely on the estimation of the left ventricular outflow tract (LVOT) cross-sectional area. Although DI estimation is straightforward, its outcome implications have never been tested in the context of routine clinical practice.

METHODS This analysis includes 488 patients with preserved (≥50%) ejection fraction and no or minimal subjective symptoms, diagnosed with ≥ mild AS. DI was computed as the ratio of the LVOT time-velocity integral to that of the aortic valve jet, and on the basis of the correlation with peak aortic jet velocity, the population was divided into 3 groups: DI <0.20, DI 0.20 to 0.25, and DI >0.25.

RESULTS The 5-year survival free of events (death or need for aortic valve replacement) was 56 ± 3% for DI >0.25, 41 ± 6% for DI 0.20 to 0.25, and 22 ± 5% for DI <0.20 (p for trend <0.001). The risk of events increased linearly with DI <0.25 (adjusted hazard ratio [HR]: 1.14; 95% confidence interval [CI]: 1.05 to 1.29) per 0.05 DI decrement; p = 0.015). On multivariable analysis, compared with patients with DI >0.25, those with DI 0.20 to 0.25 and those with DI <0.20 incurred an excess risk of events (adjusted HR: 1.65; 95% CI: 1.20 to 2.27 for DI 0.20 to 0.25 vs. DI >0.25, and adjusted HR: 2.62; 95% CI: 1.90 to 3.63 for DI <0.20 vs. DI >0.25). The association of DI and outcome was consistent in subgroups, with no interaction between DI outcome prediction and LVOT diameter, body surface area, or index stroke volume (all p for interaction ≥0.10)

CONCLUSIONS Our results demonstrate that the DI is a simple and reliable marker of AS severity with clear prognostic implications. DI <0.25 is associated with an excess risk of events after diagnosis; therefore, this cutoff should be used for AS severity assessment and for therapeutic decisions. (J Am Coll Cardiol Img 2015;8:766–75)

Severe aortic stenosis (AS) represents a contemporary health issue with a serious impact on health care providers. Elective surgery is recommended for severe symptomatic AS and for some groups in asymptomatic individuals with severe AS and preserved left ventricular ejection fraction (EF) (1,2). When transvalvular flow is normal, severe AS is diagnosed in patients with peak aortic jet velocity ≥4 m/s, mean Doppler gradient (MDG) ≥40 mm Hg, aortic valve area (AVA) <1 cm^2 (<0.6 cm^2/m^2), and dimensionless index (DI) <0.25 (1,3). Although the first 2 parameters are highly influenced by the flow across the aortic valve, the calculation of the size of the functional aortic orifice by the continuity equation (4) (i.e., AVA) relies on the accurate measure of the left ventricular outflow tract (LVOT) cross-sectional area, frequently underestimated by echocardiography (5). Data showing that the form of the LVOT is often elliptical and not circular (6,7) and uncertainties regarding the best site for LVOT diameter measurement (3,8,9) in patients with severe valve calcification raise doubts over whether AVA is the best parameter for AS quantification. Moreover, a recent study (10) showed that recommended peak aortic jet velocity and MDG cutoffs do not correspond to an AVA of 1 cm^2. The DI represents the ratio of the LVOT time-velocity integral to that of the aortic valve jet (11,12), and by eliminating LVOT cross-sectional area from the continuity equation (3) overcomes some of these limitations.

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Several studies have substantiated the solid link between increased peak aortic jet velocity and dismal outcome in AS (13–16). MDG has rarely been validated as a predictor of outcome in severe AS, but shows

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

CI = confidence interval

DI = dimensionless index

EF = ejection fraction

HR = hazard ratio

LVOT = left ventricular outflow tract

MDG = mean Doppler gradient

a close correlation with peak aortic jet velocity, reflecting the same phenomenon (16,17). In some studies, AVA <1 cm^2 and indexed AVA <0.6 cm^2/m^2 have been shown to affect outcomes irrespective of peak aortic jet velocity and MDG (18), whereas other reports do not confirm this association (16,19). In contrast, the DI cutoff is based on 2 small series published in the 1980s with few supportive outcome data, so that the effectiveness of this threshold as a marker and sensitive detector of severe AS is untested.

The present study collects consecutive patients diagnosed with AS at the echocardiography laboratories of 2 French tertiary centers (Amiens and Lille) between 2000 and 2012. We hypothesized that DI is predictive of outcome after AS diagnosis and aimed to define specific DI thresholds on the basis of their association with clinical outcome.

METHODS

STUDY POPULATION. Consecutive patients ≥18 years of age diagnosed with ≥ mild AS (aortic valve calcification with reduction in systolic movements and AVA <2 cm^2) and EF ≥50%, managed medically for at least 3 months after diagnosis, were prospectively identified and included in an electronic database. We excluded: 1) patients with ≥ mild aortic and/or mitral regurgitation; 2) patients with prosthetic valves, congenital heart disease (with the exception of bicuspid aortic valves), supravalvular or subvalvular AS, or dynamic LVOT obstruction; 3) patients with angina, syncope, and heart failure symptoms; and 4) patients who denied authorization for research participation. The present analysis included 488 patients with AS who were asymptomatic or minimally symptomatic at the time of diagnosis. Symptoms were ascertained by each patient's personal cardiologist. We considered as minimally symptomatic patients presenting with atypical chest pain and elderly patients with minimal dyspnea not clearly related to AS.

A comorbidity index summating the patient's individual comorbidities was calculated (20). Coronary artery disease was defined by the presence of documented history of acute coronary syndromes, coronary artery disease previously confirmed by coronary angiography (reduction of the normal diameter ≥50% in the left main coronary artery and ≥70% in the right coronary, left anterior descending, and circumflex arteries), or history of coronary revascularization.

We obtained Institutional Review Board authorizations before conducting the study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive Doppler-echocardiographic study using commercially available ultrasound systems. Peak aortic velocity was recorded using continuous-wave Doppler in several acoustic windows (apical 5-chamber view, right parasternal, suprasternal, epigastric). The highest aortic velocity was used to calculate aortic time-velocity integral and MDG. Pulsed Doppler LVOT velocity was recorded in the apical 5-chamber view with the sample volume at 5 mm proximal from the plane of the aortic valve. The alignment of both pulsed- and continuous-wave Doppler was optimized to be parallel with the flow. Pressure gradients were calculated using the simplified Bernoulli equation (21). AVA was calculated by the continuity equation (4). The DI was computed as ratio of the LVOT time-velocity integral to that of the aortic valve jet (11). Stroke volume was calculated by multiplying the area of LVOT by the outflow tract time-velocity integral and indexed to the body surface area. When patients were in sinus rhythm, 3 cardiac cycles were averaged for all measures. For patients in atrial fibrillation, 5 cardiac cycles were averaged.

Left ventricular dimensions were assessed from parasternal long-axis views by 2-dimensional–guided M-mode using the leading edge methodology at end-diastole and -systole. EF was calculated using Simpson's biplane method. Left ventricular mass was estimated by the formula on the basis of linear measurements and indexed for body surface area (22). The maximal velocity of the tricuspid regurgitation was estimated using continuous-wave Doppler.

CLINICAL DECISION AND FOLLOW-UP. After the initial medical management, treatment was conservative or surgical, as deemed appropriate by the patient's personal physician. The majority of patients were followed by clinical consultation and echocardiography in the outpatient clinics of the 2 tertiary centers. The others were followed in public hospitals or private practices by referring cardiologists working together with the tertiary centers. Information on follow-up was retrospectively obtained. Events were ascertained by direct patient interview and clinical examination and/or by repeated follow-up letters, questionnaires, and telephone calls to physicians, patients, and (if necessary) next of kin. Autopsy records and death certificates were consulted for attribution of causes of death. Median follow-up was 32.0 months (interquartile range: 8 to 58 months) and was 100% complete. The main outcome variable was the time to occurrence of the first composite endpoint, defined

as all-cause death or need for aortic valve replacement. Secondary outcomes were all-cause death and cardiac death. Clinical decisions regarding medical management and referral for surgery were made by the heart team with the approval of the patient's cardiologist in accordance with current practice guidelines.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± 1 SD or median and interquartile range, and categorical variables were summarized as frequency percentages and counts. Receiver-operating characteristic curves were used to establish the best cutoff values for DI corresponding to peak aortic jet velocities of 4 m/s and 5 m/s, according to the best sensitivity, specificity, and likelihood ratio. The study population was divided into 3 groups according to these determined cutoff values: DI >0.25 (referent group), DI 0.20 to 0.25, and DI <0.20. The relationship between the baseline continuous baseline variables and the 3 groups was explored using 1-way analysis of variance tests (for normally distributed variables) or Kruskal-Wallis tests (for non-normally distributed variables). Pearson's chi-square statistic or Fisher exact test was used to examine the association between the 3 groups and the baseline categorical variables. The significance between the referent group and the others was examined if there was a significant difference across categories. Individual differences were compared with Mann Whitney *U* tests (with Bonferroni correction for multiple comparisons) and Tukey tests for normally distributed data.

Event rates ±1 SE of the 3 groups were estimated according to the Kaplan-Meier method and compared with 2-sided log-rank tests. Univariate and multivariable analyses of time to events were performed using Cox proportional hazards models with DI as the independent variable in continuous and categorical format. We did not use model-building techniques and entered in the models covariates considered of potential prognostic impact on an epidemiological basis. These covariates were age, sex, body surface area, comorbidity index (not including age), history of hypertension, coronary artery disease, EF, and history of atrial fibrillation. The model was further adjusted for LVOT size in a second step. The proportional hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. We used penalized smoothing splines (P-splines) to illustrate the association of DI as a continuous variable and the risk of events (23). We conducted subgroup analyses to determine the homogeneity of the association of DI and the outcome variable. First, we estimated the effect of DI on the risk of events in each subgroup using a Cox univariate model, and then we formally tested for first-order interactions in Cox models entering interaction terms separately for each subgroup. We analyzed all-cause death and cardiac death in Cox proportional hazards multivariable models, while patients who exhibited competing events during follow-up were censored (as non-events) at the time of the event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for all-cause death and for cardiac death. Plots of cumulative hazard functions were used to graphically display death due to cardiac causes. Finally, to investigate whether DI has incremental value for risk prediction over classic markers of AS severity (peak aortic jet velocity and AVA), we used the Harrell C statistic in adjusted Cox proportional hazard models. In addition, 95% CIs of these C statistics were calculated by the "somersd" package in STATA version 12 (StataCorp LP, College Station, Texas) (24). All p values are the results of 2-tailed tests. Data were analyzed with SPSS version 13.0 (SPSS Inc., Chicago, Illinois) and STATA version 12 (StataCorp LP).

RESULTS

BASELINE CHARACTERISTICS. The study population consisted of 488 patients with AS who were enrolled at 2 tertiary hospitals in France (350 patients at Amiens and 138 patients at Lille) between 2000 and 2012. The median age of the population was 75.8 years (interquartile range: 66.9 to 81.9 years), and more than 50% were male (**Table 1**). All patients were asymptomatic or had minimal subjective symptoms at the time of diagnosis. Seventy percent of patients had a history of hypertension, and coronary artery disease was present in approximately one-third of patients (**Table 1**).

According to receiver-operating characteristic curve analysis, the best DI cutoff for the prediction of peak aortic jet velocity >4 m/s was 0.25 (sensitivity 85%, specificity 82%). The corresponding value for peak aortic jet velocity >5 m/s was 0.20 (sensitivity 82%, specificity 87%). On the basis of these cutoffs, the study population was divided into 3 groups: 1) DI <0.20; 2) DI 0.20 to 0.25; and 3) DI >0.25.

The study groups showed no difference in age, sex, body surface area, and frequency of coronary artery disease. Patients with DI <0.20 frequently had hypertension and a lower comorbidity index (**Table 1**). As expected, lower DI was associated with smaller AVA and higher MDG (**Table 2**). Although

TABLE 1 Baseline Demographic and Clinical Characteristics of the Study Patients According to DI

	All Patients (n = 488)	Group			p Value
		DI <0.20 (n = 86, 18%)	DI 0.20–0.25 (n = 117, 24%)	DI >0.25 (n = 285, 58%)	
Demographics, baseline data, and symptoms					
Age, yrs	75.8 (66.9–81.9)	74.4 (63.9–82.1)	75.3 (66.5–81.3)	76.1 (67.3–82.2)	0.46
Male	56.8 (277)	61.6 (53)	57.3 (67)	55.1 (157)	0.56
Body surface area, m^2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.19
Body mass index, kg/m^2	27.1 (24.2–30.1)	26.5 (23.4–29.8)	27.8 (24.6–31.2)	27.1 (24.3–30.1)	0.27
Systolic blood pressure, mm Hg	140 (125–150)	140 (120–144)	140 (122–150)	140 (128–150)	0.35
Medical history and risk factors					
Hypertension	70.3 (343)	57.0 (49)*	70.9 (83)	74.0 (211)	0.01
Smoking	28.3 (138)	27.9 (24)	31.6 (37)	27.0 (77)	0.65
Dyslipidemia	40.0 (195)	38.4 (33)	41.9 (49)	39.6 (113)	0.87
Diabetes mellitus	30.5 (149)	24.4 (21)	30.8 (36)	32.3 (92)	0.38
Coronary artery disease	24.8 (121)	27.9 (24)	26.5 (31)	23.2 (66)	0.60
History of atrial fibrillation	29.1 (142)	22.1 (19)	30.8 (36)	30.5 (87)	0.29
Charlson Comorbidity Index	2 (1–3)	1 (1–2)*	2 (1–3)	2 (1–3)	0.001

Values are mean ± 1 SD, median (interquartile range), or % (n). *p < 0.05 individual category versus DI >0.25.
DI = dimensionless index.

TABLE 2 Echocardiographic Parameters of the 3 Groups of Patients With AS According to DI

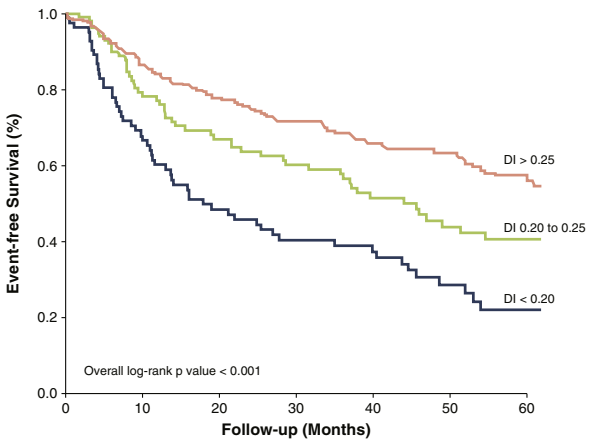
	All Patients (n = 488)	Group			p Value
		DI <0.20 (n = 86, 18%)	DI 0.20–0.25 (n = 117, 24%)	DI >0.25 (n = 285, 58%)	
Aortic valve					
AVA, cm^2	1.02 (0.8–1.38)	0.66 (0.59–0.79)*	0.86 (0.75–0.99)*	1.3 (1.1–1.5)	<0.001
Indexed AVA, cm^2/m^2	0.55 (0.42–0.70)	0.36 (0.30–0.41)*	0.45 (0.39–0.51)*	0.67 (0.58–0.78)	<0.001
Peak aortic jet velocity, m/s	3.3 (2.7–4.1)	4.5 (4.1–5.0)*	3.9 (3.4–4.4)*	2.9 (2.5–3.3)	<0.001
Transaortic mean pressure gradient, mm Hg	28 (18–41)	51 (42–65)*	37 (30–50)*	20 (15–27)	<0.001
Aortic valve velocity time integral, cm	76 (60–99)	110 (95–130)*	94 (79–109)*	63 (53–75)	<0.001
Valvulo-arterial impedance, mm Hg/ml/m^2	4.2 ± 1.3	5.0 ± 1.6*	4.4 ± 1.2*	3.9 ± 1.1	<0.001
Cardiac output					
LVOT diameter, mm	22 (20–23)	22.2 (21–24)	22 (21–23)	21 (20–23)	0.10
LVOT velocity time integral, cm	21 (18–24)	18 (15–21)*	21 (18–25)†	22 (19–24)	<0.001
Stroke volume, ml	79 (65–91)	73 (67–95)†	79 (67–95)	80 (66–94)	0.016
Indexed stroke volume, ml/m^2	41 (34–48)	39 (33–45)	41 (35–49)	42 (35–48)	0.10
Indexed stroke volume <35 ml/m^2	25.8 (126)	30.2 (26)	24.8 (29)	24.8 (71)	0.58
Cardiac output, ml/min	5.7 (4.7–6.8)	5.3 (4.4–6.4)†	5.9 (4.9–6.9)	5.8 (4.8–6.9)	0.036
LV function					
LV end-diastolic diameter, mm	49 (45–53)	49 (44–52)	50 (46–54)	49 (44–53)	0.52
LV end-systolic diameter, mm	30 (27–34)	32 (28–36)	31 (27–34)	30 (26–33)	0.13
LV end-diastolic septum thickness, mm	12 (11–14)	13 (11–14)	13 (11–14)	12 (10–14)	0.12
LV end-diastolic posterior wall thickness, mm	11 (9–12)	11 (9–13)	11 (10–13)	11 (9–12)	0.16
EF, %	65 (59–72)	63 (56–70)	65 (60–70)	65 (58–69)	0.54
LV mass, g	213 (170–264)	220 (171–279)	218 (166–261)	207 (166–249)	0.10
Indexed LV mass, g/m^2	110 (91–137)	119 (94–148)†	111 (88–137)	107 (89–129)	0.024
Other parameters					
Left atrial diameter, mm	40.6 ± 7.4	41.5 ± 7.8	40.5 ± 6.9	39.9 ± 7.5	0.47
Left atrial surface, cm^2	23.1 ± 6.4	23.7 ± 6.3	23.5 ± 7.2	22.7 ± 5.9	0.63
Systolic pulmonary artery pressure, mm Hg	30.5 (26–38)	32 (26–40)	31 (26–39)	30 (26–36)	0.25

Values are mean ±1 SD, median (interquartile range), or % (n). *p < 0.001 individual category versus DI >0.25. †p < 0.05 individual category versus DI >0.25.
AVA = aortic valve area; EF = ejection fraction; LV = left ventricular; LVOT = left ventricular outflow tract; other abbreviation as in Table 1.

LVOT size was not significantly different across the 3 DI groups, smaller LVOT time-velocity integral and lower stroke volume were associated with lower DI. Indexed left ventricular mass was greater in patients with DI <0.20 (Table 2).

PROGNOSTIC IMPLICATION OF DI. During follow-up, 241 events (117 deaths, including 54 deaths of cardiac causes, and 124 aortic valve replacements) were recorded. In patients who underwent surgery, aortic bioprostheses were used in 80% of cases (n = 99) and 45 patients had at least 1 associated coronary artery bypass graft at the time of surgery. Overall, 1-, 3-, and 5-year survival free of events was 78 ± 2%, 60 ± 2%, and 46 ± 3%, respectively. The 5-year event-free survival was 56 ± 3% for DI >0.25, 41 ± 6% for DI 0.20 to 0.25, and 22 ± 5% for DI <0.20 (p for trend <0.001) (Figure 1). On univariate Cox analysis, the risk of events increased with lower DI (HR: 1.22; 95% CI: 1.14 to 1.31 per 0.05 DI decrement) (Table 3). The relationship remained unchanged after adjustment for covariates of prognostic importance (adjusted HR: 1.24; 95% CI: 1.16 to 1.39 per 0.05 DI decrement) (Table 3). The character of the relationship between the DI as continuous variable and the risk of events during follow-up was estimated using spline functions for DI (Figure 2). On multivariable analysis, there was no increase in the risk of events with decreasing DI when it remained >0.25 (adjusted HR: 1.09; 95% CI: 0.89 to 1.24 per 0.05 DI decrement). With DI ≤0.25, there was a significant increase in the risk of events with decreasing DI (adjusted HR: 1.14; 95% CI: 1.05 to 1.29 per 0.05 DI decrement). Compared with patients with DI >0.25, those with DI 0.20 to 0.25 and those with DI <0.20 displayed an excess risk of events (HR: 1.45; 95% CI: 1.06 to 1.98; p = 0.021 for DI 0.20 to 0.25 vs. DI >0.25, and HR: 2.33; 95% CI: 1.71 to 3.18; p < 0.001 for DI <0.20 vs. DI >0.25) (Table 3). The relationships were strengthened after adjustment for covariates (adjusted HR: 1.65; 95% CI: 1.20 to 2.27; p = 0.002 for DI 0.20 to 0.25 vs. DI >0.25, and adjusted HR: 2.62; 95% CI: 1.90 to 3.63; p < 0.001 for DI <0.20 vs. DI >0.25) (Table 3, Figure 3). The full results of the multivariable models for the prediction of events during follow-up are presented in Online Table 1. In multivariable analyses, the addition of DI to the model with AVA and peak aortic jet velocity resulted in an incremental improvement in the overall performance of the model (Harrell C statistic: 0.714 vs. 0.674; p = 0.004 for AVA plus peak aortic jet velocity plus DI vs. AVA plus peak aortic jet velocity and 0.714 vs. 0.667; p = 0.002 for AVA plus peak aortic jet velocity plus DI vs. AVA alone) (Online Table 2). The association of DI ≤0.25 and risk of events was consistent in subgroups of patients with AS (Figure 4). There were no significant interactions between DI ≤0.25 and any of the subgroups.

FIGURE 1 Kaplan-Meier Event-Free Survival Curves According to DI Categories



Patients at Risk							
DI > 0.25	285	210	182	165	138	115	83
DI 0.20 to 0.25	117	73	60	52	38	27	25
DI < 0.20	86	53	37	30	25	15	9

DI = dimensionless index.

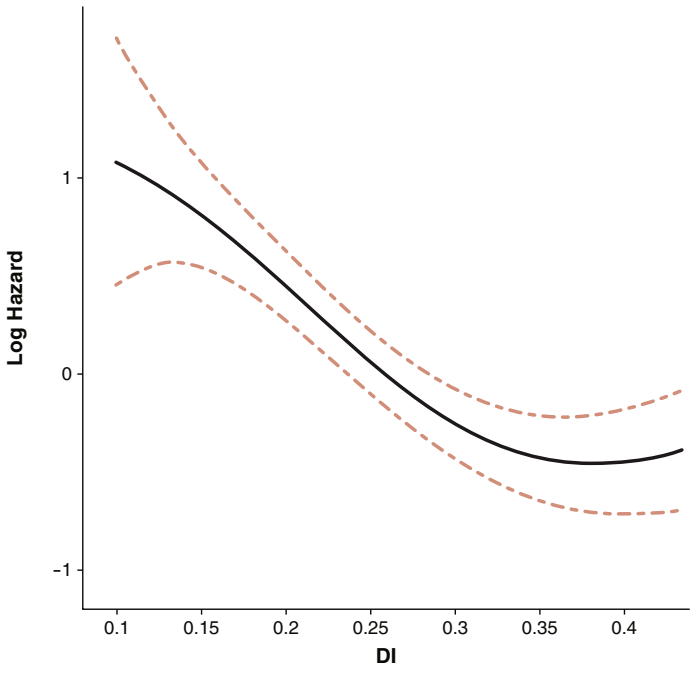
TABLE 3 Relative Risk of Events (All-Cause Death or Aortic Valve Replacement Surgery) During Follow-Up Associated With DI

	HR (95% CI)	p Value
DI categories		
Unadjusted		
DI > 0.25	Referent	
DI 0.20–0.25	1.45 (1.06–1.98)	0.021
DI < 0.20	2.33 (1.71–3.18)	<0.001
Model 1*		
DI > 0.25	Referent	
DI 0.20–0.25	1.61 (1.19–2.21)	0.004
DI < 0.20	2.50 (1.84–3.45)	<0.001
Model 2†		
DI > 0.25	Referent	
DI 0.20–0.25	1.65 (1.20–2.27)	0.002
DI < 0.20	2.62 (1.90–3.63)	<0.001
Per 0.05 decrement in DI		
Unadjusted	1.22 (1.14–1.31)	<0.001
Model 1*	1.23 (1.14–1.33)	<0.001
Model 2†	1.24 (1.16–1.39)	<0.001

*Adjustment for age, sex, Charlson comorbidity index, history of hypertension, coronary artery disease, history of atrial fibrillation, body surface area and left ventricular ejection fraction. †Adjustment for age, sex, Charlson comorbidity index, history of hypertension, coronary artery disease, history of atrial fibrillation, body surface area, left ventricular ejection fraction, and left ventricular outflow tract diameter. Charlson comorbidity index does not include age.

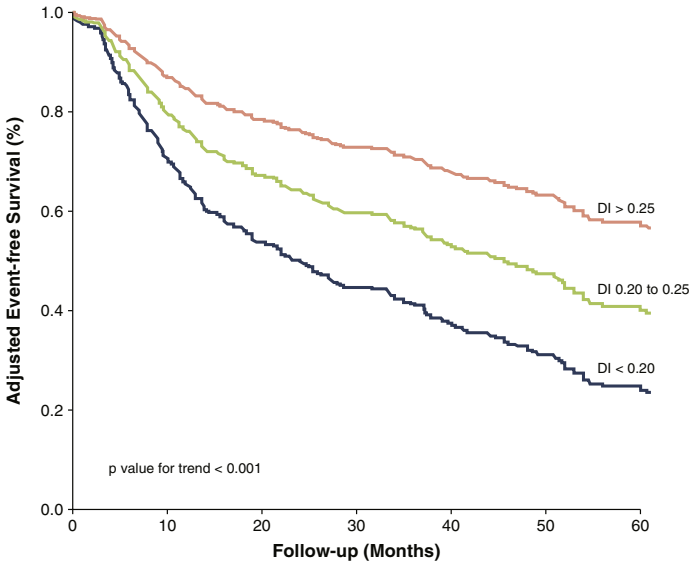
CI = confidence interval; DI = dimensionless index; HR = hazard ratio.

FIGURE 2 Relationship Between DI and Risk of Events During Follow-Up



Hazard ratio **(solid line)** and 95% confidence intervals **(dashed lines)** are estimated in a Cox model with DI represented as a spline function and adjusted for age, sex, comorbidity index, coronary artery disease, hypertension, atrial fibrillation, ejection fraction, body surface area, and left ventricular outflow tract. DI = dimensionless index.

FIGURE 3 Adjusted Curves of Event-Free Survival According to DI Categories



Curves are adjusted for age, sex, comorbidity index, coronary artery disease, hypertension, atrial fibrillation, ejection fraction, body surface area, and left ventricular outflow tract size. DI = dimensionless index.

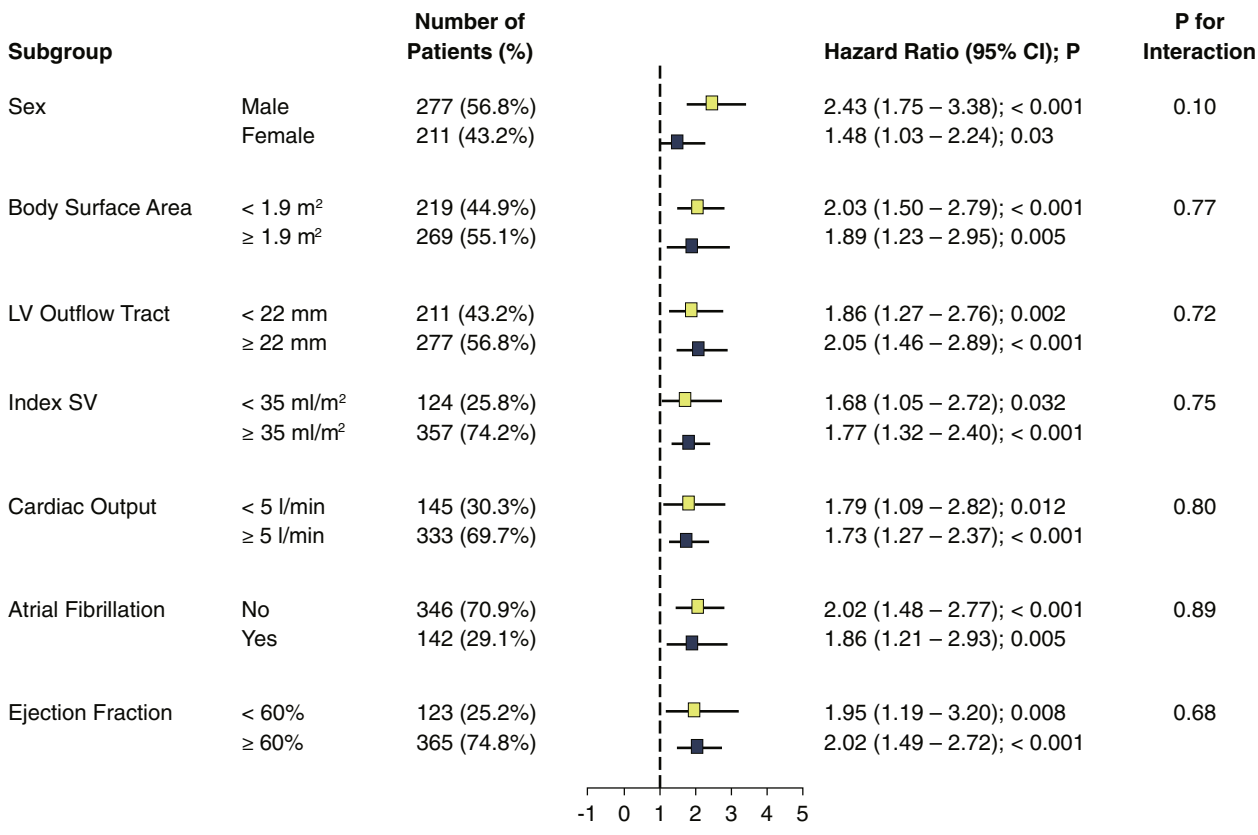
On multivariable analysis, DI ≤0.25 was not associated with a significantly greater risk of all-cause death during follow-up (adjusted HR: 1.23; 95% CI: 0.78 to 1.96; p = 0.37). However, with DI ≤0.25, there was a significant increase in the risk of cardiac death compared with DI >0.25 (adjusted HR: 2.08; 95% CI: 1.06 to 4.11; p = 0.034) (Figure 5).

DISCUSSION

To the best of our knowledge, this is the first study to specifically assess the outcome implication of DI in a large population of patients with AS and preserved EF irrespective of mean pressure gradient. According to our results, DI independently predicts the occurrence of events (death or aortic valve replacement) and cardiac death after AS diagnosis. The prognostic impact of DI was powerful, because after adjustment for age, sex, comorbidity, coronary artery disease, EF, LVOT size, and other variables of prognostic importance, each 0.05 DI decrement was associated with an approximately 25% increase in the risk of all-cause death or need for aortic surgery. Moreover, we observed an abrupt increase in the risk of events below the 0.25 cutoff, suggesting that from a prognostic point of view, DI ≤0.25 truly defines severe AS. Finally, the DI performs well in subgroups of patients with AS, with no interaction between its prognostic power and sex, body surface area, LVOT size, or stroke volume.

Peak aortic jet velocity and MDG are the cornerstones of AS severity assessment (1,2). In patients with normal transvalvular flow and calcified aortic valves, the sole detection of a peak aortic jet velocity ≥4 m/s establishes the diagnosis of severe AS. In the last American Heart Association/American College of Cardiology guidelines on valvular heart disease, AVA appears as a second-line parameter, of special interest in cases with low transvalvular flow (2). Both parameters have limitations and should be viewed as complementary in a multiparametric strategy of AS severity assessment (25). Peak aortic jet velocity and MDG are influenced by volume flow rate. Moreover, accurate recording of peak aortic jet velocity requires parallel alignment between the continuous Doppler ultrasound beam and the aortic flow, nonparallel intercept angle leading to underestimation of AS severity. In regard to the calculation of the AVA by the continuity equation, it is subject to errors because of the notoriously difficult measure of the LVOT cross-sectional area. First, from a theoretical standpoint, the assumption that the cross-sectional area is circular has not been confirmed by recent echocardiography and computed tomography studies (6,7,26). On the

FIGURE 4 HR and 95% CI for Risk of Events Associated With DI ≤0.25 in Subgroups of Patients With AS



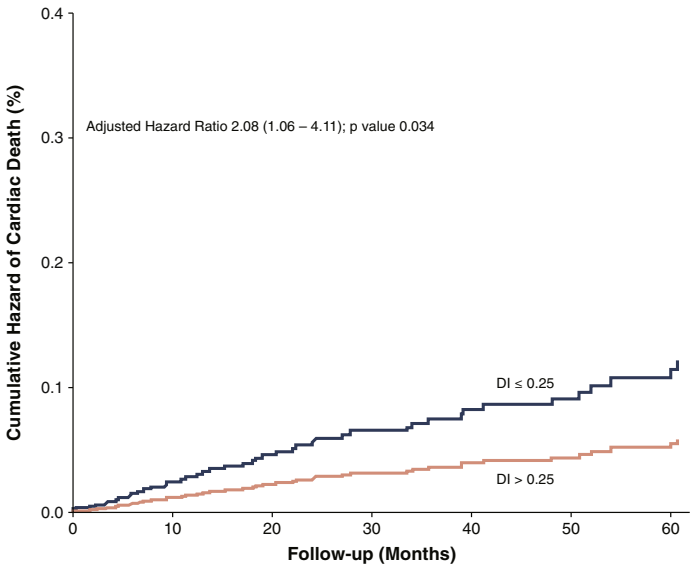
AS = aortic stenosis; CI = confidence interval; DI = dimensionless index; HR = hazard ratio; LV = left ventricular; SV = stroke volume.

other hand, from a practical point of view, an accurate measure of the LVOT size by 2-dimensional echocardiography is elusive in patients with massive calcification of the aortic annulus or in case of a poor acoustic window. Finally, the best site for LVOT size measurement is still debated (3,8,9). Although guidelines recommend a mid-systole measurement from the septal endocardium to the anterior mitral leaflet parallel to the aortic plane, 5 to 10 mm below the valve orifice (3), current practice generally uses simpler, yet reliable measures of LVOT diameter at the level of aortic cusp insertion (9,12).

DI represents the ratio of the LVOT time-velocity integral to that of the aortic valve jet (11,12). In a study of 48 patients with AS undergoing cardiac catheterization, Otto et al. (11) reported that DI showed better sensitivity than Doppler pressure gradient to identify severe AS (97% vs. 81%). Subsequently, Oh et al. (12) reported a similar correlation between anatomic AVA and Doppler-derived AVA calculated with time-velocity integral ratio or peak velocity ratio and proposed 0.25 as the velocity ratio cutoff to identify severe AS. This index has the potential advantage to be independent of a patient's body surface area (3) and is not influenced by the estimation of the LVOT cross-sectional area. Current guidelines recommend the 0.25 DI cutoff to define severe AS (1,3).

Several studies have validated the outcome implications of the different Doppler-derived parameters for AS severity assessment. The prognostic impact of peak aortic jet velocity in AS has been well demonstrated (13–16). Otto et al. (13) reported an inverse relationship between peak aortic jet velocity and outcome in asymptomatic AS. In asymptomatic patients with very severe AS, Rosenhek et al. (16) observed that higher peak aortic jet velocity is related to a pejorative outcome. MDG has rarely been validated as a predictor of outcome in severe AS, but it shows a close linear correlation with peak aortic jet velocity (10,17), reflecting the same phenomenon. The impact of AVA on outcome is somewhat less clearly

FIGURE 5 Cumulative Hazard of Cardiac Death According to DI Categories (≤0.25 and >0.25)



Curves are adjusted for age, sex, comorbidity index, coronary artery disease, hypertension, atrial fibrillation, EF, body surface area, and LVOT size. Abbreviations as in Figures 1 and 2.

established. Although some studies reported that AVA <1 cm^2 and indexed AVA <0.6 cm^2/m^2 strongly affect outcome, irrespective of peak aortic jet velocity and MDG (18), others fail to identify a link between AVA and outcome (16,19). We demonstrate the link between the 0.25 DI cutoff previously proposed and recommended by guidelines and the occurrence of events in a large population of patients with AS. We also show that patients with AS with DI <0.20 correspond in terms of outcome to very severe AS, as defined by Rosenhek et al. (16). Furthermore, we show that the prediction of events in patients with AS and preserved EF is best achieved by a combination of severity markers, such as AVA, peak aortic jet velocity, and DI, which strongly suggests the value of a multiparametric approach, especially in difficult cases. Although previous studies have suggested that the DI cutoff for severe AS is variable according to LVOT diameter (27), our analysis shows that the prognostic implication of DI is not affected by LVOT diameter, body surface area, and stroke volume. Thus, DI might be particularly useful in patients in whom the estimation of the LVOT cross-sectional area is difficult. Our findings are in accordance with a recent subanalysis of the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial showing that DI is strongly associated with valve-related events in asymptomatic patients with severe low-gradient AS and preserved EF (28). This index remains to be tested in patients with low-flow, low-gradient AS and preserved EF, in whom the rate of measurement inconsistencies is considerable.

STUDY LIMITATIONS. Information on follow-up was retrospectively obtained, and therefore, our study has the inherent limitations of such analyses. The specific indications for surgery during follow-up were not collected in our database. However, diagnosis and follow-up were performed by cardiologists with expertise in valvular disease, and the surgical decisions were made by the heart team with the approval of the patients' physicians in accordance with current practice guidelines. For this analysis, we included patients with AS and no symptoms or minimal subjective manifestations. Indeed, we consider that among elderly patients with AS, it is often difficult to differentiate asymptomatic individuals from patients who have minimal subjective manifestations. Patients were enrolled at the time of baseline echocardiography, and medical treatment at baseline was not systematically recorded. We acknowledge that medical therapy might affect outcomes in this cohort of patients with AS with various degrees of severity. Finally, we would like to point out that we studied exclusively asymptomatic and minimally symptomatic patients with AS with preserved EF and without significant valve regurgitation. Further studies are needed to evaluate the role of DI in other subsets of patients with AS.

CONCLUSIONS

This analysis of a large registry of valvular AS in routine clinical practice shows that the DI is a valuable parameter in defining the severity of AS and in predicting the occurrence of events after diagnosis. The risk of events increases linearly with DI decreasing below the 0.25 cutoff and is considerable in patients with DI <0.20. Therefore, DI seems useful to identify severe AS with poor prognosis and might help to reconcile discordant results between valve area and pressure gradient. These findings support the widespread use of this simple and reliable parameter for AS severity assessment and for therapeutic decisions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The DI represents an easily obtainable prognostic marker for characterizing the severity of AS. The risk of cardiac events after AS diagnosis increases linearly with DI <0.25 cutoff and is considerable with DI <0.20.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The DI should be measured in all patients with AS and used as a severity marker and for outcome prediction. Because assessment of DI does not require the measurement of LVOT cross-sectional area, errors related to the measurement of the LVOT area can be easily circumvented.

TRANSLATIONAL OUTLOOK: The prognostic value of DI does not seem to be influenced by sex, body surface area, LVOT size, or stroke volume. Prospective studies are needed to test the value of the DI in patients with low-flow, low-gradient AS and preserved EF, in whom measurement errors may be frequently encountered.

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KEY WORDS aortic stenosis, dimensionless index, echocardiography, outcome

APPENDIX For supplemental tables, please see the online version of this article.

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